REMARKS

Claims 53-59, 67-68, 71-72 and 79-81 were pending in the application. In the Office Action dated August 25, 2004, claims 53, 55, 56, 67, 71 and 79-81 were rejected, and claims 54, 57-59, 68 and 72 were objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. In the instant Amendment, claims 53-55, 57-59, 67-68, 71-72 and 79-81 have been amended to clarified the invention. Upon entry of the above-made amendment, claims 53-59, 67-68, 71-72 and 79-81 will be pending.

Claim 53 has been amended to recite that the diagnostic profile *comprises measurements of a first plurality of cellular constituents* (emphasis added). Support for the amendment is found in the specification at, e.g., page 18, lines 7-8; page 20, lines 11-16 and FIG.1. Claim 53 has been amended to recite that *said interpolated perturbation response profile comprising measurements of said first plurality of cellular constituents* extracted from perturbation response curves of *said measurements as a function of level of said perturbation to said protein* (emphasis added). Support for the amendment is found in the specification at, e.g., page 18, lines 13-16 and lines 24-27; page 22, lines 10-24 and FIG. 2; page 27, lines 10-14; page 28, line 19 through page 30, line 10. Claim 53 has also been amended to recite that the interpolated perturbation response curves are obtained by a method comprising: (i) providing perturbation response profiles of said protein for said cell type, wherein *each* said perturbation response profile comprises *measurements of a second plurality of cellular constituents* in a cell of said cell type at *one of* a plurality of discrete levels of perturbation to said protein, and (ii) interpolating *measurements of each cellular constituent of said second plurality in* said perturbation response profiles *over said plurality of discrete levels of said perturbation to obtain a perturbation response curve of said cellular constituent* so that an interpolated perturbation response profile comprising measurements of said first plurality of cellular constituents may be extracted *at a level* over a range of levels of perturbation to said protein (emphasis added). Support for the amendments can be found in the specification at page 18, lines 4-16 and lines 24-27; page 22, lines 10-24 and FIG. 2; page 24, lines 20-26; page 27, lines 10-14; page 28, line 19 through page 30, line 10 and FIG. 4; and page 74, line 1 through page 76, line 26. Claims 67, 71 and 79-81 have been amended similarly. The claims dependent on these claims have also been amended so that there is appropriate antecedent basis.

No new matter has been added by these amendments. Entry of the foregoing amendments and consideration of the following remarks are respectfully requested.

THE REJECTION UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 53, 55, 56, 67, 71 and 79-81 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Tice et al., U.S. Patent No. 6,024,983 ("Tice"). Applicants respectfully disagree with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383, U.S. 1 (1956). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The presently claimed invention provides computer systems and computer program products for determining a level of activity of (or a level of perturbation to) a protein or other biologically active cellular constituent. As described in the specification at page 13, lines 13-15 and lines 24-26, an activity of a cellular constituent refers to effects of the cellular constituent on the state of a biological system, e.g., the state of cells of a cell type. Similarly, a perturbation to a cellular constituent also manifests itself as changes in the states of cells (see, e.g., the instant specification at page 16, lines 15-18). The biological state of a cell as used in the specification refers to the state of a collection of cellular constituents, which are sufficient to characterize the cell for an intended purpose (see, e.g., the instant specification at page 14, lines 26-30). Thus, Applicants respectfully point out that the presently claimed computer systems and programs are for determining the effects mediated by a cellular constituent on the state of a biological system (e.g., a type of cell). In the presently claimed invention, the activity of a cellular constituent on the state of a cell of a cell type is represented by a profile, e.g., a diagnostic profile, comprising measurements of a plurality of cellular constituents in a cell of the cell type (see, e.g., the instant specification at page 14, line 24 through page 15, line 19; page 18, lines 7-8 and lines 13-16). This diagnostic profile is used by the computer systems and programs of the invention to determine the level of

activity of the cellular constituent. The computer systems and program products of the invention make use of perturbation response curves, which are obtained from a set of measured perturbation response profiles, each of which comprises measurements of the cellular constituents in a cell subjected to one of a plurality of discrete levels of perturbation to the cellular constituent of interest (see, e.g., the instant specification at page 18, lines 4-16). Perturbation response profiles corresponding to levels of perturbation not coinciding with the plurality of discrete levels represented by the measured perturbation response profiles are obtained by interpolating the set of measured perturbation response profiles (see, e.g., the instant specification at page 18, lines 16-18). The claimed computer systems and program products carry out the method of determining an activity level of a cellular constituent by determining, among the above mentioned measured or interpolated perturbation response profiles, a perturbation response profile whose similarity to the diagnostic profile is the greatest, and taking the level of perturbation of this perturbation response profile as the level of activity of the cellular constituent represented by the diagnostic profile (see, e.g., the instant specification at page 18, lines 28-32).

Tice teaches a method of delivering a bioactive agent, e.g., a vaccine, to an animal involving the steps of encapsulating effective amounts of the agent in a biocompatible excipient to form microcapsules having a size less than approximately ten micrometers and administering effective amounts of the microcapsules to the animal (Tice, Abstract). Tice teaches a radioimmunoassay for evaluating the effect of administration of a trinitrophenyl (TNP) hapten (Trinitrophenyl-Keyhole Limpet Hemocyanin) in generating an immune response in animals (Tice, col. 6, lines 36-67). Tice teaches that for assaying TNP specific antibodies, calibrations were made using serial twofold dilutions of a standard serum containing known amounts of immunoglobulin on wells coated with 1 microgram/well isotype-specific antibodies. Calibration curves and interpolation of the amount of antibodies generated in response to the administration of a TNP hapten were then obtained using the calibration measurements.

Applicants respectfully submit that Tice merely teaches using interpolation of calibrations to determine the abundance of an antibody. Tice does not teach or suggest a diagnostic profile and perturbation response profiles each comprising *measurements of a plurality of* cellular constituents, much less determining a level of perturbation to a cellular constituent, e.g., a protein, using such perturbation response profiles. Applicants respectfully

point out that it is clear from the specification of the instant application that a diagnostic profile or a perturbation response profile as used in the claims refers to a profile containing a plurality of data points, each data point being for one cellular constituent (see, e.g., specification at page 28, lines 3-18, and page 17, line 5, through page 18, line 2), the plurality of data points being for a plurality of different cellular constituents. For example, FIG. 1 of the specification illustrates a response profile comprising measurements of changes in expression levels of different genes in cells of a yeast mutant. In the Office Action, the Examiner contends that there is no instant limitation that limits these profiles to "different" cellular constituents (see, page 3 of the Office Action). Applicants have amended the claims to recite that the diagnostic profile comprises measurements of a first plurality of cellular constituents and each perturbation response profile comprises measurements of a second plurality of cellular constituents. In contrast, Tice teaches assaying an amount of antibodies generated in an animal in response to the administration of an antigen, and as such, does not teach assaying the state of a cell by measuring a plurality of cellular constituents in the cell. In addition, Tice teaches the use of calibrations, which were made using serial twofold dilutions of a standard serum containing known amounts of immunoglobulins. Such calibrations are not perturbation response profiles comprising measurements of a plurality of cellular constituents in a cell at a plurality of levels of a perturbation to the cellular constituent whose activity is of interest. As such, interpolation of calibrations in Tice is not interpolation of perturbation response profiles. Therefore, Tice does not teach or suggest representing an activity of a cellular constituent using a diagnostic profile comprising a first plurality of cellular constituents. Tice does not teach or suggest perturbation response profiles each comprising a second plurality of cellular constituents. Tice does not teach or suggest determining, among measured or interpolated perturbation response profiles, a perturbation response profile whose similarity to the diagnostic profile is the greatest, and taking the perturbation level of this perturbation response profile as the activity level of the cellular constituent represented by the diagnostic profile. Therefore, Applicants respectfully submit that Tice does not render the presently claimed invention obvious, and that the rejection of claims 53, 55, 56, 67, 71 and 79-81 under 37 C.F.R. § 103 (a) based on Tice should be withdrawn.

THE OBJECTION TO CLAIMS 54, 57-59, 68 AND 72 SHOULD BE WITHDRAWN

Claims 54, 57-59, 68 and 72 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claim. Since, as discussed above, the base claims are not rendered obvious by Tice, the dependent claims 54, 57-59, 68 and 72 also are not rendered obvious by Tice. The objection to claims 54, 57-59, 68 and 72 should therefore be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted,

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